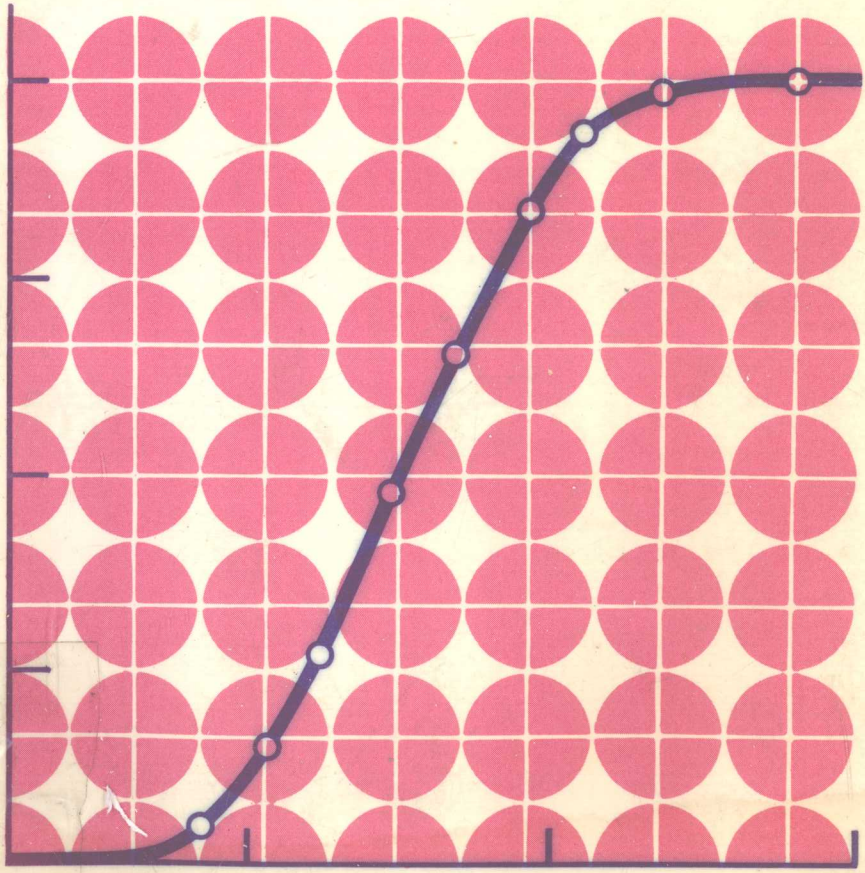
John L. Reid, Peter C. Rubin, Brian Whiting

Lecture Notes on Clinical Pharmacology

Second Edition



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Lecture Notes on Clinical Pharmacology

JOHN L. REID
DM FRCP
Regius Professor of Materia Medica

PETER C. RUBIN
DM MRCP
Wellcome Trust Senior Fellow

BRIAN WHITING
MD FRCP
Reader in Clinical Pharmacology
Department of Materia Medica
University of Glasgow

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Preface

Clinical pharmacology is a new and rapidly expanding specialty which has grown in importance with the increase in both the number and the complexity of drugs. Bridging the gap between laboratory science and the practice of medicine at the bedside, clinical pharmacology has as its primary aim the promotion of safe and effective drug use: to optimise benefits and minimise risks.

Developments in medicine, pharmacology and physiology have led to a better understanding of disease processes and a more rational use of drugs. Recent years have seen the development of drugs designed to interact with specific receptors or enzyme systems. In addition the application of biochemical and immunological techniques has led to a clearer appreciation of the mechanisms involved in adverse drug reactions and interactions. With this understanding has come the potential to reduce greatly the number of unwanted drug effects. The intensity of drug action is often related to plasma concentration, and recent advances in analytical techniques have enabled rapid and accurate determination of the plasma concentrations of many drugs. This provides an added dimension to the optimisation of drug use.

For many years we have taught clinical pharmacology to medical practitioners and undergraduate students. We were persuaded by our students that there was a need for a brief, clearly written and up to date review of clinical pharmacology. *Lecture Notes on Clinical Pharmacology* was prepared to meet this need. In this second edition we have incorporated developments which have occurred in clinical pharmacology since the preparation of the first edition in 1981. Five chapters have been rewritten and several others revised. We have not attempted to be comprehensive, but have tried to emphasise the principles of clinical pharmacology, areas which are developing rapidly and topics which are of particular clinical importance. The book is based on the course of lectures and seminars in clinical pharmacology and therapeutics for medical students at the University of Glasgow. In addition, we have drawn on our experience of organising courses for postgraduate students, general practitioners and medical specialists. Thus, while intended primarily for medical students, we believe this book will also be of use to those preparing for higher examinations and doctors in established practice who wish to remain well informed of current concepts in clinical pharmacology.

For all who use it, we hope this book will provide a clear understanding not only of *how* but also of *when* to use drugs.

John Reid
Peter Rubin
Brian Whiting

Glasgow, January 1985

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We ourselves accept full responsibility for the contents of the volume and for any mistakes or misunderstandings.

John Reid
Peter Rubin
Brian Whiting

Contributors

The following contributed substantially to the writing of chapters in this book.

Professor K.C. Calman	Department of Clinical Oncology Glasgow University	Cytotoxic drugs
Professor W.S. Nimmo	Department of Anaesthetics Western Infirmary Glasgow	Anaesthetics and relief of pain
Professor D.H. Lawson	Department of Medicine Royal Infirmary Glasgow	Adverse drug reactions

Colleagues from the Department of Materia Medica and Therapeutics at Glasgow University contributed to the following chapters:

Dr G.J. Addis	Drugs and respiratory disease
Dr B.C. Campbell	Self poisoning
Dr H.L. Elliott	Corticosteroids
Dr W.F.M. Fulton	Heart failure and angina pectoris
Dr W.S. Hillis	Cardiac arrhythmias
Dr C.W. Howden	Drugs and gastrointestinal disease

Contents

SECTION 1

CHAPTER 1

Principles of Clinical Pharmacology

Until the twentieth century, medical practice depended largely on the administration of mixtures of natural plant or animal substances. These preparations contained a number of pharmacologically active agents in variable amounts. Their actions and indications were empirical and based on historical or traditional experience. Their use was rarely based on an understanding of the mechanism of disease or careful critical measurement of effect.

During the last 80 years, an increased understanding of biochemical and pathophysiological factors in disease has developed. The chemical synthesis of agents with well characterized, specific actions on cellular mechanisms has led to the introduction of many powerful and effective drugs.

1.1 PRINCIPLES OF DRUG ACTION

Pharmacological agents are used in therapeutics to:

1. Cure disease:
   chemotherapy in cancer or leukaemia,
   antibiotics in specific bacterial infections
2. Alleviate symptoms:
   antacids in dyspepsia,
   non-steroidal anti-inflammatory drugs in rheumatoid arthritis
3. Replace deficiencies:
   restoration of normal function by the replacement of a deficiency in an endogenous hormone, enzyme or transmitter.

A *drug* is a single chemical entity that may be one of the constituents of a medicine.

A *medicine* may contain one or more active constituents (drugs) together with additives to facilitate administration (colouring, flavouring, and other excipients).

Mechanisms of drug action

Action on a receptor

A receptor is a specific macromolecule, usually a protein, to which a specific group of drugs or naturally occurring substances such as neurotransmitters or hormones can bind.

An *agonist* is a substance which stimulates or activates the receptor to produce an effect.

An *antagonist* prevents the action of an agonist but does not have any effect itself unless it also possesses *partial agonist* activity.

The biochemical events which result from an agonist–receptor interaction and which produce an effect are still to be determined.

There are many types of receptors and in several cases subtypes have been identified which are also of therapeutic importance (Table 1.1).

Table 1.1 Some receptors involved in the action of commonly used drugs

Receptor	Subtype	Main actions of natural agonist	Drug agonist	Drug antagonist
Adrenoceptor	α_1	Vasoconstriction		Prazosin
	α_2	Hypotension, sedation	Clonidine	
	β_1	↑ Heart rate	Dopamine, Dobutamine	Atenolol, Metoprolol
	β_2	Bronchodilation Vasodilation	Salbutamol, Terbutaline	
		Uterine relaxation	Ritodrine	
Cholinergic	Muscarinic	↓ Heart rate		Atropine
		↑ Secretion		Benzotropine
		↑ Gut motility		Orphenadrine
		↓ Urinary sphincter tone		
		↑ Eye muscle tone		
	Nicotinic	Contraction of striated muscle		Suxamethonium, Tubocurarine
Histamine	H_1	Bronchoconstriction, Capillary dilation		Chlorpheniramine, Promethazine
	H_2	↑ Gastric acid		Cimetidine, Ranitidine
Dopamine		CNS Neurotransmitter	Bromocriptine	Chlorpromazine, Haloperidol, Thioridazine
Opioid		CNS Neurotransmitter	Morphine, Pethidine, etc	Naloxone

Action on an enzyme

Enzymes, like receptors, are protein macromolecules with which substrates interact to produce activation or inhibition. Drugs in common clinical use which exert their effect through enzyme action generally do so by inhibition:

Digoxin inhibits the membrane bound Na^+/K^+ ATPase
Aspirin inhibits prostaglandin synthetase
Captopril inhibits angiotensin converting enzyme
Phenelzine inhibits monoamine oxidase
Carbidopa inhibits decarboxylase
Allopurinol inhibits xanthine oxidase

Drug receptor antagonists and enzyme inhibitors can act as *competitive, reversible antagonists* or as *non-competitive irreversible antagonists*. The duration of the effect of drugs of the latter type is much longer than that of the former. Effects of competitive antagonists can be overcome by increasing the dose of endogenous or exogenous agonist while effects of irreversible antagonists cannot usually be overcome.

Propranolol is a competitive beta-adrenoceptor antagonist used in hypertension and angina. Its effects last for hours and can be overcome by administering an appropriate dose of a beta-receptor agonist like isoprenaline.

Phenelzine is an irreversible non-competitive monoamine oxidase inhibitor used in depression. Its action and adverse effects may persist for two to three weeks.

Action on membrane ionic channels

The conduction of impulses in nerve tissue and electromechanical coupling in muscle depend on movement of ions, particularly sodium calcium and potassium, through membrane channels. Several groups of drugs interfere with these processes:

Antiarrhythmic drugs (Chapter 6),
Calcium slow channel antagonists (Chapter 8),
General and local anaesthetics (Chapter 17),
Anticonvulsants (Chapter 19).

Cytotoxic actions

Drugs used in cancer or in the treatment of infections may kill malignant cells or micro-organisms. Often the mechanisms have been defined in terms of effects on specific receptors or enzymes. In other cases chemical action (alkylation) damages DNA or other macromolecules and results in cell death or failure of cell division.

Dose–response relationship

Dose–response relationships in clinical practice rarely follow the classical sigmoid pattern of experimental studies. It is uncommon for the upper plateau or maximum effect to be reached in man or to be relevant therapeutically. Dose–response relationships may be *steep* or *flat*. The former implies a marked

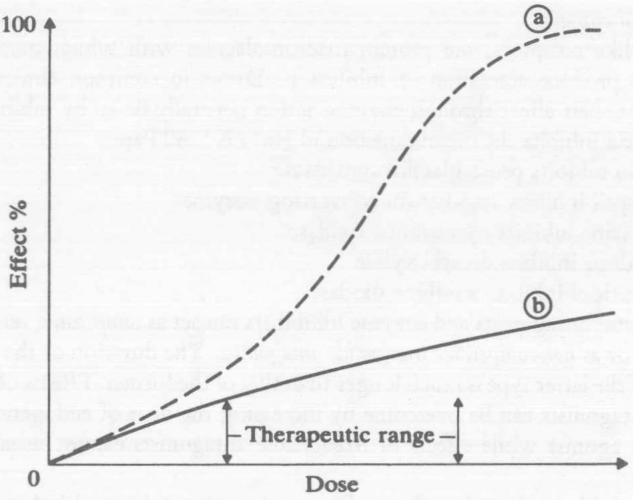

Fig. 1.1 Schematic example of a drug (a) with a steep dose–response relationship in the therapeutic range, e.g. warfarin as an oral anticoagulant and (b) a flat dose–response relationship within the therapeutic range, e.g. thiazide diuretics in hypertension.

increase in response with modest increases in dose while the latter implies little increase in response over a wide dose range (Fig. 1.1).

The *potency* of a drug is relatively unimportant — what matters is its *efficacy* or the maximum effect that can be obtained.

In clinical practice the maximum therapeutic effect may often be unobtainable because of the appearance of adverse or unwanted effects: few, if any, drugs cause a single pharmacological response. The dose–response relationship for adverse effects is often different in shape and position to that of the therapeutic dose–response relationship. The difference between the dose which will produce the desired effect and that which will cause adverse effects is called the *therapeutic index* and is a measure of the selectivity of a drug (Fig. 1.2).

The shape and position of *dose–response* curves in a group of patients is variable because of genetic, environmental and disease factors. But this variability is not solely an expression of differences in response to drugs. It has two important components, the *dose–plasma concentration* relationship and the *plasma concentration–effect* relationship:

$$\text{Dose} \rightarrow \text{Concentration} \rightarrow \text{Effect}$$

With the development of specific and sensitive chemical assays for drugs in body fluids, it has been possible to characterize the dose–plasma concentration relationship in individual patients so that this component of the variability in response can be largely accounted for. This is *pharmacokinetics* (Chapter 1.2), and its application in clinical practice is *clinical pharmacokinetics* (Chapter 2). The

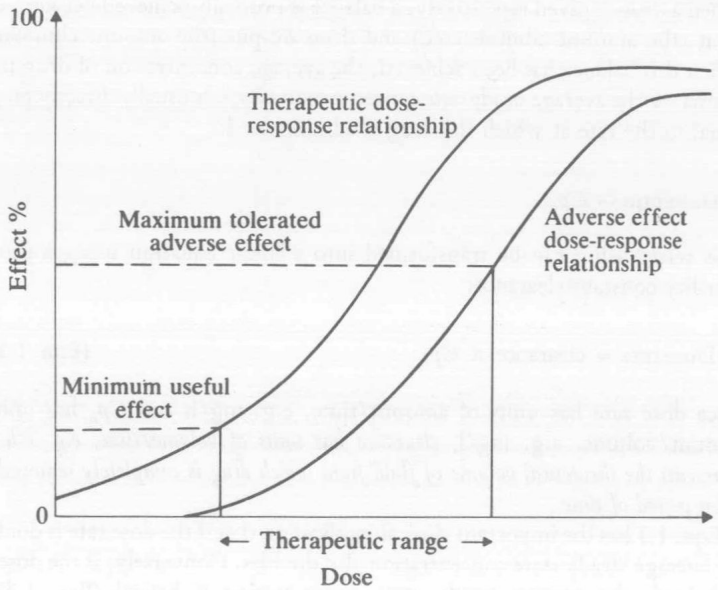

Fig. 1.2 Schematic diagram of the dose–response relationship for the desired effect (therapeutic dose–response) and for an undesired adverse effect. The therapeutic index is the extent of displacement of the two curves within the therapeutic range of dose.

residual variability in the dose–response relationship — characterized by the concentration–effect component — is a true expression of drug response, or in quantitative terms, a good measure of the *sensitivity* of a patient to a drug. This is the province of pharmacodynamics and the exploration of the factors which underlie the variability in both pharmacokinetics and pharmacodynamics is the basis of clinical pharmacology.

1.2 PHARMACOKINETICS

Pharmacokinetics describes *what the body does to a drug*: pharmacodynamics describes *what a drug does to the body*. A grasp of basic pharmacokinetic principles leads to a better understanding of the design of dosage regimens and their adjustment in disease states. The essence of pharmacokinetics is that it describes mathematically the movement of a drug into and out of the body so that the amount of drug (the dose) required to produce a desired effect can be determined. Two fundamental concepts underlie these calculations — *clearance*, which deals with the body's ability to eliminate a drug, and *volume of distribution* which deals with the apparent space into which a drug distributes after it has been administered.

Clearance

When a drug is given repetitively, a balance is normally achieved between drug input (the amount administered) and drug output (the amount eliminated). When this balance has been achieved, the average concentration of drug in the plasma, or the average *steady state* concentration (Cp_{ss}), is usually directly proportional to the rate at which the drug is administered:

$$\text{Dose rate} \propto Cp_{ss}$$

This relationship can be transformed into a linear equation using a proportionality constant clearance:

$$\text{Dose rate} = \text{clearance} \times Cp_{ss} \qquad \text{(Eqn. 1.1)}$$

Since dose rate has units of amount/time, e.g. mg/h and Cp_{ss} has units of amount/volume, e.g. mg/l, *clearance has units of volume/time, e.g. l/h, and represents the theoretical volume of fluid from which drug is completely removed in a given period of time.*

Eqn. 1.1 has the important clinical implication that if the dose rate is doubled, the average steady state concentration also doubles. Conversely, if the dose rate is halved, the average steady state concentration is halved (Fig. 1.3). In pharmacokinetic terms, this is referred to as a first order, or linear process, and results from the fact that the rate of elimination is proportional to the amount of drug present.

Clearance depends mostly on the efficiency with which the liver and/or the kidneys can eliminate a drug. It may be altered in disease states, and if necessary, can be calculated from rearrangement of Eqn. 1.1:

$$\text{Clearance} = \frac{\text{Dose rate}}{Cp_{ss}} \qquad \text{(Eqn. 1.2)}$$

Since Cp_{ss} is the *average* plasma concentration at steady state, it represents the *average* value of the concentration throughout a dosage interval. If a drug is administered orally, Cp_{ss} may be approximated by the concentration which is one third of the way between the minimum and maximum concentrations in a dosage interval (Fig. 1.4).

After oral administration a drug may not be completely absorbed. The dose rate used in these calculations, therefore, should be reduced by a factor that accounts for the proportion of drug that is actually absorbed, i.e. its bioavailability — designated F — with a value ranging from 0 to 1.0. Eqn. 1.2 then becomes

$$\text{Clearance} = \frac{F \times \text{Dose rate}}{Cp_{ss}} \qquad \text{(Eqn. 1.3)}$$

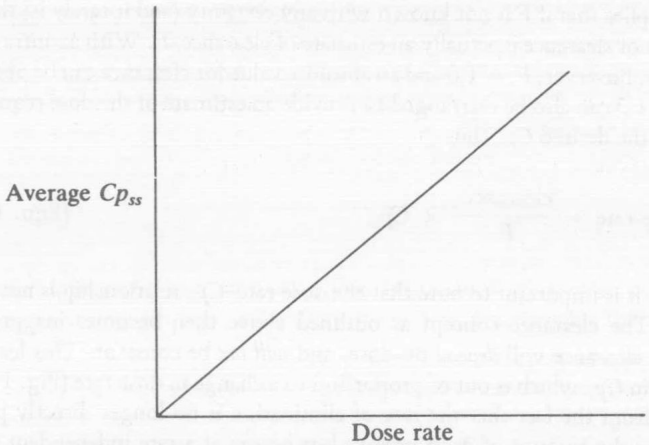

Fig. 1.3 The dose rate/steady state concentration relationship where drug clearance is a first order, or linear process.

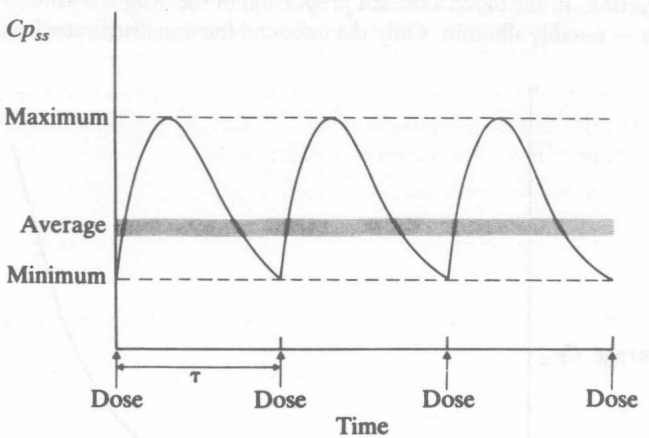

Fig. 1.4 Plasma concentration — time profile during repetitive oral administration of a drug. The profile oscillates between maximum and minimum concentrations: τ is the dosage interval. An approximation of the average Cp_{ss} is shown as the shaded horizontal line.